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An International Association For Pharmaceutical Science And Technology

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US Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Ref.: FDA White Paper *"Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model"* submitted to Docket #2003N-0059 - Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach

Dear Sir/Madam:

PDA is pleased to provide these comments on the White Paper issued September 2004, entitled *"Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model."* PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological and device manufacturing and quality.

PDA is encouraged by the Agency's efforts to move ahead with this program to aid in the fulfillment of one of the goals of *Pharmaceutical CGMPs for the 21st Century*, which is to maximize the Agency's limited resources while providing the most health promotion and protection at the least cost for the public. PDA supports the approach and process that the Agency is taking and agrees this model should be implemented now and modified as improvements are identified. The following list of comments and conclusions reached by the PDA is provided to the Agency for consideration of inclusion in this program.

Point #1
Risk Filtering and Model Summary
In the section "Risk Filtering and Model Summary" it is stated "FDA does not intend to publish or disclose such details of a site's individual score or ranking". Without a site knowing the factors that were considered in their risk ranking, the site will not have the benefit of the agency's analysis in order to focus on those areas representing the highest risk. It is PDA's opinion a site should not have to guess if they have been determined to be high risk and what factors put them in that category. Incorrect assumptions could occur and continuous improvement opportunities might be missed. One theme of the Quality Systems Approach to Pharmaceutical CGMP Regulations is to encourage dialogue between the agency and industry, which will make it easier for process changes to be made as both parties learn more about the products and processes in use. One feedback loop to accomplish this outcome would be to engage in active discussion regarding the data derived from this Risk Ranking Model. Optimally, transparency between the agency and industry regarding the data used to rank an individual company should exist. Such transparency

dialog develops that will help determine a true assessment of the severity of individual risk factors and their probability of occurrence.

Under "Future Revisions" changes under consideration include incorporating more active mitigating risk factors, such as process capability metrics for each site's product line, and other indicators of process understanding and control. PDA would like to encourage taking this step towards transparency in this program so that both the Agency and industry may gain a greater understanding of products and processes so as to have the greatest positive impact on public health.

Point #2
Analysis of Data to Present and Moving Forward
Another concern regarding the execution of this system is the possibility of erroneous conclusions because of lack of data used to develop the risk factors. Two statements in this document lead to the concern there may have been a higher emphasis on opinion rather than fact for complex processes for which there has not been an abundance of data, or total lack of data. Additional transparency between the Agency and industry would help to mitigate some of industry's concerns. The statements that have generated these concerns are the following:

1. The agency acknowledges that many potential risk factors were excluded because of the lack of data or other data limitations. *(Ref. section: Implementation of the Model and Risk Estimation).*
2. Regarding the weighing and ranking of risk factors the paper states "Although the Agency lacks specific databases to answer these questions, the Agency has a large number of staff with expertise in this area." *(Ref. section: Process Component)*

PDA will be more than willing to participate in industry and industry association dialogue to help augment the database in a spirit of transparency and continuous improvement.

Point #3
Facility Component
Included in the risk-ranking model for the "Facility Component" is an estimate of the volume of production output, with higher volume and production output resulting in higher weights. This factor is not self-explanatory or as simple as presented in the white paper. PDA feels strongly neither higher individual batch volumes nor greater numbers of products automatically mean greater risk. A site can become adept at changeovers when they perform this task routinely and thus the site may have best practices instead of a risk factor. Additionally, high volumes of individual products may result in a better understanding of the processes involved and therefore result in greater control and less risk to the public. This assumption of a direct correlation between higher volumes and higher risk could be a misleading assumption. It is again recommended that the Agency provide a higher level of transparency to industry regarding assessment of risk so measures taken by an individual site to ameliorate their risks can be incorporated into the algorithm used by the Agency to rank a given site.

PDA seeks clarification regarding the History of Inspection factor of the Facility Component of the risk-ranking model. There is concern about the inclusion of pre-approval inspection data to determine site risk. This data may lend complexity to a site profile that may not be truly relevant in the context of biennial CGMP inspections. PDA considers only relevant issues from PAI inspections, those within a CGMP context, should be considered for inclusion into the risk ranking of a site.

Additionally, there is also concern that inspection data for sites under a consent decree, where a third party audits under the auspices of the FDA, would be included in the database for risk ranking. The purpose of generating third party consent degree data is different from the data generated from a CGMP inspection performed by the FDA. PDA feels this data should not be included.

In conclusion, PDA feels that with additional transparency between FDA and industry, the implementation of risk-based approaches for prioritizing CGMP inspections of pharmaceutical manufacturing sites will serve to focus both industry and Agency attention on critical areas. It is crucial that the most accurate and pertinent data is used and again PDA offers to participate in dialogue with the agency and other industry association groups to ensure the best model is implemented. This dialogue would be especially important for risk models that are derived from a minimum amount of information or partial data sets. Additionally, this document does not comment on the applicability of this approach to CBER regulated products therefore, PDA would like to see some mention of this under Future Revisions.

Yours sincerely,

Victoria Ann Dedrick
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PDA